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(10) Shirley E. Freeman

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REPORT

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ACTIONS OF LIDOCAINE ON ATRIAL AND NODAL TRANSMEMBRANE POTENTIALS IN GUINEA PIG AND RABBIT

Shirley E. Freeman

ABSTRACT

Effects of lidocaine (1 x 10^{-5}M to 4 x 10^{-5}M) have been determined on transmembrane potentials recorded in guinea pig left atrium and in sinoatrial and atrioventricular nodes of the rabbit heart. The first time derivative of the action potential was displayed as a function of membrane voltage, forming a phase-plane trajectory. A number of parameters of the action potential were determined from the trajectory. Lidocaine reduced the maximum rate of rise of the atrial potential and slowed repolarization. Propagation velocity was reduced, as was maximum ionic conductance. These effects were markedly dependent on the stimulation rate. Variation in the external K^+ and Ca^{2+} levels also altered the response to lidocaine. However, relative to appropriate controls these effects were still seen. Atrioventricular nodal potentials were slightly depressed; at 5 Hz the node showed 2:1 block, and perinodal cells were recruited to the functional node. The sinoatrial node showed a decrease in the rate of slow diastolic depolarization, and a slight decrease in spike height.

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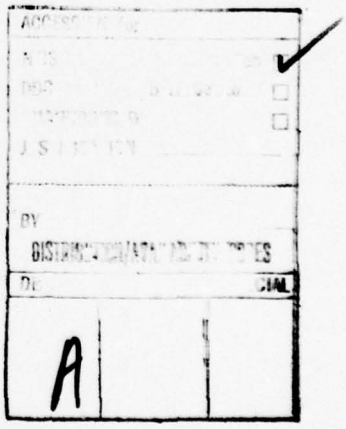

ACTIONS OF LIDOCAINE ON ATRIAL AND NODAL TRANSMEMBRANE POTENTIALS IN GUINEA PIG AND RABBIT

INTRODUCTION

The electrophysiological effects of lidocaine have been investigated extensively (for a review see Sasyniuk and Ogilvie (1975)). In general isolated preparations of Purkinje fibres have received most attention, however ventricular muscle cells and atrial cells have also been studied (Davis and Temte, 1969; Singh and Vaughan Williams, 1971; Mandel and Bigger, 1971). The results obtained by different workers have not always been similar, nor have they been easily related to the antiarrhythmic effects of the drug in the human. Some of the reasons for these discrepancies have been discussed by Rosen and Hoffman (1973). Briefly these reasons include the likelihood that lidocaine has different effects on the different specialised cell systems of the heart, and the observation that variation in the external electrolyte solution modifies the actions of lidocaine. Authors have used nutrient solutions with different K^+ or Ca^{2+} levels. More intractable difficulties are related to the problem of devising an animal model which can be related to the diseased human myocardium.

The present investigation has attempted to elucidate the effect of frequency of stimulation on the actions of lidocaine on atrial and nodal cells. In addition, the external potassium level has been varied over the range that is likely to occur in moderate electrolyte disturbances, to ascertain the effect of change of diastolic potential on the actions of lidocaine. Some experiments with raised Ca^{2+} levels were also included, since many authors have used higher levels than is our custom.

The upstroke of the atrial action potential of the guinea pig was investigated by recording its first time derivative (dV/dt), and displaying this derivative as a function of membrane voltage to form a phase-plane trajectory (Jenerick, 1963, 1964; Paes de Carvalho *et al*, 1969; Freeman and Turner, 1974 a and b). A number of parameters of the action potential have been calculated from the phase-plane trajectory, and these were found to be altered in a characteristic way by doses of lidocaine which are comparable with those used clinically (Sasyniuk and Ogilvie, 1975). An evaluation of the effect of lidocaine on sinoatrial and atrioventricular nodal action potentials was carried out on a preparation isolated from the rabbit heart, since a comparable *in vitro* study of the AV node is lacking.

MATERIALS AND METHODS

Atrial preparations were dissected from the hearts of New Zealand rabbits weighing from 1.5 - 2.2 kg, or from guinea pigs (200 - 300 g) as described previously (Freeman and Turner, 1974 b). Rabbit atrial preparations included the sinoatrial and atrioventricular nodes, and were spontaneously active. Quiescent preparations of left guinea pig atrium were prepared from the atrial appendage. The preparations were pinned (with the endocardial surface uppermost) to a silicon rubber sheet which covered the bottom of the organ bath. Preparations were stimulated when required with platinum pin electrodes. Rectangular pulses of 0.3 ms duration were adjusted to 1.5 times threshold. The order of change of stimulation rate was randomised.

Transmembrane potentials were recorded with microelectrodes filled with 3M KCl (Freeman and Turner, 1970), with a d.c. resistance of from 10 - 20 megohms. The action potential was recorded as a function of time, and the first time derivative, dV/dt, was recorded as a function of membrane voltage. The phase-plane trajectory which resulted was displayed on the oscilloscope at right angles to the voltage-time signal (Freeman and Turner, 1974 a and b). Conduction velocity along bands of pectinate muscles was determined from the latency of the photographed spike potential. The distance from the stimulating cathode to the recording microelectrode was measured with a calibrated eyepiece grid in the dissecting microscope.

Preparations were bathed with nutrient solution in a non-recirculating system. The solution had the following composition: NaCl 115 mM, KCl 4.6 mM, $CaCl_2$ 1.8 mM, $MgSO_4$ 1.2 mM, NaH_2PO_4 1.2 mM, $NaHCO_3$ 22 mM and glucose 22 mM. The solution was bubbled continuously with 95% O_2 - 5% CO_2 and was maintained at 37°C. As required the K^+ or Ca^{2+} level was varied without a compensating change in the level of Na^+. Lidocaine hydrochloride (Xylocard, Astra) was added to the solution perfusing the preparation for 30 - 40 min before readings were taken. Control penetrations were obtained before and 60 - 70 min after the drug was washed out of the bath. On changing the K^+ level of the perfusate 5 min was allowed for the changed diastolic potential to stabilise. It was usually possible to determine the effects of two stimulus frequencies or two drug levels on each preparation. The data obtained was pooled for each group of experiments and analyzed by means of Students "t" test. Each observation was obtained by penetration of a different fibre. It was usual to track across the preparation to obtain a representative sample of atrial cells.

RESULTS

Actions of lidocaine on the guinea pig atrium

The effects of lidocaine on guinea pig atrial potentials were investigated in three groups of experiments. In the first of these the effects of different concentrations of lidocaine were investigated at 0.5 Hz, 2 Hz and 5 Hz. In the second group the effects of variation in external K^+ level on lidocaine action were determined at a drug concentration of 2×10^{-5}M. One group of experiments was carried out at 2 Hz, another group was carried out at 0.5 Hz and 5 Hz. Thirdly, the action of lidocaine was studied in high K^+ plus high Ca^{2+} solutions.

Table 1 shows that the maximum rate of rise of the action potential was consistently reduced by lidocaine over the whole frequency range. Repolarization was also consistently slowed. Spike height was reduced by lidocaine (1×10^{-5}M - 4×10^{-5}M) at 2 Hz, but not at 0.5 Hz or 5 Hz. There was also a tendency for the maximum diastolic potential to be reduced at 2 Hz. There was a significant reduction in conduction velocity at 4×10^{-5}M lidocaine at all frequencies. This reduction was also significant at 2×10^{-5}M lidocaine at 5 Hz.

Table 2 shows the results obtained from the analysis of the phase-plane trajectories. The rationale for the analysis has been reported previously (Freeman and Turner 1974 a and b, 1975). If it is assumed that the atrium exhibits cable behaviour (Hodgkin and Rushton, 1946) a number of membrane constants can be calculated from the data obtained from the trace. The rate constant of the rising phase of the trajectory, k_1, equals $2R_iC\theta^2/a$ where R_i is the internal resistance of the muscle fibre, C is the specific membrane capacitance, θ is the conduction velocity and a is the fibre radius (Jenerick 1963, 1964). These assumptions have been considered by de Beer *et al* (1976) who note the requirements for a minimum distance between stimulating and recording electrodes. Lidocaine consistently reduced k_1, as would be expected from the reduction in conduction velocity which was noted in Table 1. Measurement of conduction velocity in the atrium is subject to error, because of its branching syncytial structure. It is likely that changes in k_1 may more accurately reflect changes in conduction velocity.

A significant reduction in k_2, the rate constant of the falling arm of the trajectory was also observed. The membrane ionic conductance, g_i, was calculated from these two rate constants (Jenerick, 1963), according to the relation :

$$g_i = C(k_2/k_1) \quad (k_2 + k_1)$$

A constant value for C, the membrane capacitance, of $2\mu f/cm^2$ was used throughout (Freeman and Turner, 1974 b). Lidocaine brought about a reduction in g_i at concentrations $\geq 2 \times 10^{-5}$M at all frequencies. It will be noted that values for k_2 are not given at 5 Hz for lidocaine 2×10^{-5}M, and k_1

and k_2 are not shown at 5 Hz for lidocaine 4 x 10^{-5}M. This is because in these instances the trajectories showed marked upwards concavity, which precluded the estimation of the rate constants. Thus g_i was so reduced that it could not be estimated. The action potential height was however not reduced (in fact slightly increased) by lidocaine at 5 Hz. This appeared to be due to an increase in the slow component of inward current, which carried the action potential to its maximum voltage (Paes de Carvalho *et al*, 1969). The excitation potential, V^*, of the propagated spike was not altered by lidocaine. Similarly V_{max}, the membrane potential at which the rate of rise of the spike is greatest, was not consistently altered.

The second two groups of experiments were concerned with the effects of variation in external K^+ levels on lidocaine actions. Tables 3 and 4 show the effects of a low K^+ level. As would be expected (Weidmann, 1955; Freeman, 1974) reduction in external K^+ hyperpolarized the atrium, and brought about concomitant increases in spike potential and rate of rise, without altering the rate of repolarization. The rate constants k_1 and k_2 increased significantly. The ionic conductance showed an increase which was not significant. Relative to these data, lidocaine + 2.3 mM K^+ showed a highly significant reduction in the rate of rise of the spike and the overshoot. In low K^+ solution lidocaine did not decrease the rate of repolarization. The rate constants k_1 and k_2 were reduced relative to the low K^+ solution without lidocaine, but the decrease in g_i was again not significant. The excitation potential, V^*, was more negative in low K^+ solution than in the controls, but was unaltered by the addition of lidocaine. The third line of results in Table 4 confirms the actions of lidocaine relative to controls that are shown in Table 1. Thus relative to the appropriate control lidocaine causes a similar reduction in the maximum rate of rise of the spike in low K^+ solutions to that seen at the physiological K^+ level.

Similarly, an increase in K^+ level to 6.9 mM, as is shown in Tables 5 and 6 depolarized the preparation, reduced spike height and rate of rise, but did not alter the duration of the action potential. Addition of lidocaine to this solution brought about the usual reduction in rate of rise of the spike, increased the duration and reduced the ionic conductance.

These two experiments were carried out at a stimulus frequency of 2 Hz. The *in vivo* rate of the guinea pig heart is approximately 5 Hz. Consequently, the experiments in which the level of K^+ was raised were repeated at 0.5 and 5 Hz, to ascertain if the combined high K^+-lidocaine effect was frequency dependent. The experimental design was similar to that shown in Tables 5 and 6. Relative to controls in K^+ 4.6 mM the effect of 6.9 mM K^+ resembled that seen at 2 Hz. The preparations were depolarized, and the spike height, overshoot and maximum rate of rise were reduced. These changes were more marked at 5 Hz than at 0.5 Hz. The effects of lidocaine were closely similar to those already reported in Tables 1 and 2. A comparison of lidocaine in 6.9 mM K^+ solution at 0.5 Hz, showed that diastolic potential and spike height were unaltered by lidocaine, but the maximum rate of rise was reduced from 127 ± 6.0 Vs^{-1} (24 observations) to 110 ± 4.7 Vs^{-1} (24 observations); this difference was significant at P=0.04. The time to 50% repolarization was unchanged, as were the excitation potential and V_{max}. Both k_1 and k_2 were reduced significantly, however the reduction in g_i was not significant. Similar results were obtained at 5 Hz. The maximum rate of rise was

reduced from 72 ± 3.6 Vs^{-1} (21 observations) to 54 ± 3.6 Vs^{-1} (32 observations), this difference was significant at P = 0.002. The duration of the action potential increased; 50% repolarization was 32 ± 0.9 ms in 6.9 mM K^+ and 37 ± 0.9 ms in lidocaine + 6.9 mM K^+ (P = 0.003). The rate constant k_1 declined from 3.3 ± 0.2 ms^{-1} to 2.8 ± 0.1 ms^{-1} (P = 0.02). The second rate constant, k_2, could not be identified as a linear segment in the phase-plane trajectory at this frequency, either with or without lidocaine. However, in spite of the reduction in g_i which this implies, the preparations were able to follow a stimulus rate of 5 Hz. It appears that conduction is slowed, but is maintained by the slow component of the action potential.

Further experiments were carried out in which both the K^+ and Ca^{2+} levels of the nutrient solution were raised. Relative to potentials recorded in 6.9 mM K^+ (1.5 times normal) the increase in Ca^{2+} to 3.6 mM (2 times normal) caused a 5 mV increase in spike height and a small but significant increase in rate of rise of the spike without alteration in diastolic potential. The duration of the action potential was slightly reduced. Tables 7 and 8 show the effect of lidocaine (2×10^{-5}M) in a solution with raised K^+ and Ca^{2+}. Lidocaine reduced spike height and rate of rise, but did not increase the duration of the action potential. The rate constant, k_1, was significantly reduced, suggesting a decrease in conduction velocity, but k_2 was not altered. Consequently the ionic conductance was not altered by lidocaine in this solution.

Actions of lidocaine on the rabbit atrioventricular node

Most studies of lidocaine in humans have indicated that atrioventricular conduction is not affected except in cases of diffuse conduction disturbance (Sasyniuk and Ogilvie, 1975). Potentials recorded in the isolated rabbit preparation were but little altered at the spontaneous rate of the rabbit atrium (Table 9). Lidocaine (2×10^{-5}M or 4×10^{-5}M) reduced spike height, overshoot and rate of rise of the action potential, and prolonged it. The last named effect may be ascribed partly to the reduction in rate brought about by the drug, however the increased duration at 4×10^{-5}M is proportionately greater, for a similar rate change. At the higher drug concentration the maximum diastolic potential was also reduced.

The spontaneous rate of the isolated preparation is however much less than *in vivo*. Consequently experiments were carried out in preparations which were stimulated at 5-6 Hz. The stimulating electrodes were placed either on the atrial appendages or on the superior vena cava in the region of the sinoatrial node. The results were similar in both cases. As was noted previously (Freeman and Turner, 1974 b), the atrioventricular node will follow stimulating frequencies of 5-7 Hz. The rate of rise and the duration of the action potential are reduced at high frequencies (Table 10). In the presence of 2×10^{-5}M lidocaine all the cells of the node showed 2:1 block. The characteristics of the action potential were similar to the controls without lidocaine, but it was not possible to find cells which could follow the driving frequency. Cells adjacent to the His bundle also followed the reduced rate, which suggested that the node was not showing any pacemaker activity. Experiments were carried out in which the recording microelectrode was moved out of the AV node into the adjoining tissue near the orifice of the coronary sinus. Retrograde tracking from the lower node

through the N region (Paes de Carvalho *et al*, 1969) failed to reveal any cells which would follow the driving frequency. However, tracking from the node into the venous tissue between the coronary sinus and the interatrial septum revealed a progression in action potential characteristics. Some cells followed the driving stimulus with alternating large and small action potentials. Some followed the stimulus intermittently, periods of 2:1 block were interspersed with periods of full transmission of the impulse. In other cells small action potentials with an amplitude less than the diastolic potential were recorded, which followed the driving frequency. In these cells the upstroke of the action potential was frequently notched, and the phase-plane trajectory suggested the presence of two components of inward current. Prior to the addition of lidocaine to the perfusate or after its withdrawal these cells showed the electrical characteristics of transition cells. The action potentials had greater amplitude and rates of rise than nodal cells, but rather lower than those of atrial cells. The diastolic potential was intermediate between the two cell types. Lidocaine appeared to recruit cells to the functional AV node from this transition area. All these effects of lidocaine were reversible on washing the tissue in nutrient solution for 60-80 min.

Actions of lidocaine on the rabbit sinoatrial node

Pacemaker activity of the sinoatrial node was slowed by lidocaine at 2×10^{-5}M and 4×10^{-5}M. This effect could be correlated with a reduction in spike height, overshoot and rate of rise. At 2×10^{-5}M the maximum diastolic potential was unaffected but at 4×10^{-5}M this parameter was significantly reduced. These results are set out in Table 11. It is of some interest that the action potential duration was not increased by lidocaine, in spite of the slowing of the pacemaker activity (Freeman and Turner, 1974 b). At the higher drug level an attempt was made to penetrate perinodal cells between the sinostrial node and the ring bundle. There was no evidence of a selective depression of electrical characteristics in such cells. These results differ from those of Mandel and Bigger (1971) chiefly in that effects were seen at lower dose levels of lidocaine. It is possible that this may be related to the lower level of K^+ (3 mM) in the perfusion solution used by Mandel and Bigger.

DISCUSSION

The actions of lidocaine on the guinea pig atrial preparation are consistent with the hypothesis that lidocaine reduces the fast component of inward current which is carried by sodium ions (Singh and Vaughan Williams, 1971). In terms of the Hodgkin-Huxley hypothesis lidocaine interfers with depolarization by altering the voltage at which the sodium depolarizing system can be reactivated after repolarization. Thus inactivation of the sodium current mechanism is prolonged in time. This theory is consistent with the observed frequency dependence of the changes in rate of rise and ionic conductance brought about by lidocaine. The drug is more effective at rates of 5 Hz than at 0.5 Hz; this effect was also noted by Tritthart *et al*, (1971). However the action potential is still propagated at 5 Hz, even when the ionic conductance is markedly reduced. This may be due to an augmentation of the slow inward component of current, which is carried by calcium

or calcium + sodium ions. Carmeliet (1975) has reported evidence suggesting interaction between the fast and slow components of inward current, whereby reduction in Na^+ conductance increases Ca^{2+} conductance, which may not normally be fully activated. The duration of the action potential was increased by lidocaine at all frequencies studied, which may also be related to the increased flow of slow component current. It is noteworthy however that this effect was not seen in the presence of 2.3 mM K^+ solution; it may be assumed that the increased diastolic potential has interfered with activation of this current. Relative to the appropriate controls lidocaine has otherwise a similar action regardless of the diastolic potential. The absolute magnitude of the rate of rise is greater in low than in high K^+ solutions, but is still reduced compared with lidocaine-free controls in high or low K^+ solution. It is noteworthy however that increase in both K^+ and Ca^{2+} levels prevented the increase in action potential duration. There are clearly important interactions between diastolic potential, Ca^{2+} level and slow component activation, which should be investigated further, and which may explain discrepancies in results from different laboratories.

Thus high stimulation rates, lidocaine and reduction in the diastolic potential all interfere with activation of the sodium system. All of these therefore reduce the rate of rise of the spike, ionic (sodium) conductance, and conduction velocity. In the presence of all three conditions however the atrium still propagated action potentials. This would suggest that impulses will be transmitted through the atrium in cases of atrial flutter, even in the presence of high levels of external K^+. In view of this the actions of lidocaine on the atrioventricular node are of some importance. Lidocaine at concentrations up to 4×10^{-5}M, which must be considered as high in the therapeutic dose range (Sasyniuk and Ogilvie, 1975), does not markedly depress nodal action potentials at the spontaneous rate of the isolated preparation. However, when a stimulus rate of 5.5 Hz was applied to the atrium in the presence of lidocaine the AV node showed 2:1 block. It was noted also that transition cells near the orifice of the coronary sinus showed electrical characteristics like those of nodal cells in the presence of lidocaine, so that the effective area of the node was increased. Should such a phenomenon obtain in the human heart it is possible that it would block a tendency for circus movement around the base of the great veins.

There would appear to be qualitative differences between the actions of lidocaine on atrial tissue and on ventricular and Purkinje cells. Many authors have noted a shortening of action potential duration in the latter cell types, which is consistent with the finding of Arnsdorf and Bigger (1975) of an increase in membrane potassium conductance caused by lidocaine in long Purkinje cell preparations. These authors suggested that the decreased cardiac excitability brought about by the drug is due to an increase in the liminal length, which is the area of membrane required to be raised above threshold to provide local circuit current sufficient to elicit an action potential.

The effects of lidocaine on the sinoatrial node may be interpreted in terms of a change in both inward and outward currents. At 2×10^{-5}M lidocaine the slow diastolic depolarization which produces the pacemaker potential is reduced, spike height and overshoot are also less than in controls. Reduction in the sodium/calcium permeability may be the chief

effect at this level. However at 4×10^{-5}M lidocaine the maximum diastolic potential is also reduced. In conjunction with the failure of the action potential to be prolonged by a rate decrease this may suggest an increase in potassium permeability. Should this be so the SA node would appear to respond to the drug in a different manner to atrial cells.

Further work will be required to determine whether the apparently different actions of lidocaine on the atrium and on ventricular tissue are indeed genuine, or are related to species differences or differences in technique. The present study emphasises the sensitivity of the rate of repolarization to moderate changes in electrolyte concentration.

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TABLE 1

THE EFFECT OF RATE OF STIMULATION ON LIDOCAINE ACTION ON ATRIAL POTENTIALS

Rate Hz	Spike height mV	Max. diastolic potential mV	Overshoot mV	Max. rate of rise Vs^{-1}	Time to 50% repolarization ms	Conduction velocity $cm\ s^{-1}$
0.5 control	89.8 ± 1.1 (43)	69.4 ± 0.7 (43)	20.4 ± 0.8 (43)	178 ± 5.0 (43)	37 ± 0.7 (43)	63 ± 0.9 (24)
lidocaine (2×10^{-5}M)	92.8 ± 1.3 (35) P = 0.09	73.1 ± 1.3 (34) P = 0.02	19.8 ± 0.9 (34) P = 0.6	160 ± 5.4 (35) P = 0.02	40 ± 0.3 (35) P < 0.001	64 ± 1.5 (13) P = 0.6
lidocaine (4×10^{-5}M)	90.6 ± 2.4 (20) P = 0.6	71.8 ± 1.7 (20) P = 0.2	18.8 ± 1.0 (20) P = 0.3	139 ± 7.2 (20) P < 0.001	40 ± 0.8 (20) P = 0.007	53 ± 0.9 (20) P < 0.001
2 control	93.3 ± 0.8 (101)	74.2 ± 0.6 (101)	19.1 ± 0.6 (101)	187 ± 4.7 (101)	35 ± 0.5 (97)	75 ± 3.2 (20)
lidocaine (1×10^{-5}M)	85.1 ± 1.3 (41) P = 0.001	68.1 ± 1.1 (41) P = 0.001	17.0 ± 0.6 (41) P = 0.6	149 ± 7.1 (41) P < 0.001	44 ± 0.6 (39) P < 0.001	82 ± 2.1 (22) P = 0.06
lidocaine (2×10^{-5}M)	86.7 ± 1.2 (58) P = 0.001	69.2 ± 0.9 (58) P = 0.001	17.5 ± 0.6 (58) P = 0.1	139 ± 5.7 (58) P < 0.001	44 ± 0.4 (57) P < 0.001	78 ± 1.9 (41) P = 0.4
lidocaine (4×10^{-5}M)	86.8 ± 1.0 (64) P = 0.001	69.8 ± 1.1 (63) P = 0.001	17.0 ± 1.0 (63) P = 0.05	122 ± 4.1 (64) P < 0.001	39 ± 0.5 (64) P < 0.001	67 ± 1.0 (20) P = 0.001
5 control	77.6 ± 1.3 (33)	67.0 ± 1.1 (33)	10.6 ± 1.1 (33)	112 ± 4.9 (33)	32 ± 1.2 (33)	51 ± 0.5 (22)
lidocaine (2×10^{-5}M)	78.4 ± 1.9 (38) P = 0.7	66.2 ± 1.0 (38) P = 0.7	12.2 ± 1.0 (38) P = 0.3	84 ± 5.3 (38) P < 0.001	40 ± 1.1 (38) P < 0.001	40 ± 0.9 (14) P < 0.001
lidocaine (4×10^{-5}M)	80.5 ± 3.2 (18) P = 0.3	72.2 ± 1.2 (18) P = 0.02	8.3 ± 1.6 (18) P = 0.2	76 ± 5.9 (18) P < 0.001	40 ± 1.2 (18) P < 0.001	24 ± 0.7 (18) P < 0.001

Pooled data from eight guinea pigs. Values are shown ± S.E.M. P values refer to significance of difference of means using Students "t" test. The number of observations is shown in parenthesis.

TABLE 2

THE EFFECT OF RATE OF STIMULATION ON LIDOCAINE ACTION ON SOME PARAMETERS OF THE ATRIAL POTENTIAL

Rate Hz	Rate constant, k_1, ms^{-1}	Rate constant, k_2, ms^{-1}	Ionic conductance, g_i, mmho cm^{-2}	Excitation potential V* mV	V_{max} mV
0.5 control	6.7 ± 0.1 (18)	5.1 ± 0.2 (18)	18.2 ± 0.8 (18)	-53 ± 1.2 (18)	-32 ± 0.8 (18)
lidocaine (2×10^{-5}M)	5.2 ± 0.2 (22) P < 0.001	4.1 ± 0.2 (22) P < 0.001	14.9 ± 0.2 (22) P = 0.02	-57 ± 1.2 (21) P = 0.02	-36 ± 1.2 (21) P = 0.01
lidocaine (4×10^{-5}M)	6.0 ± 0.2 (19) P = 0.009	4.0 ± 0.2 (19) P < 0.001	13.4 ± 0.9 (19) P < 0.001	-55 ± 1.1 (19) P = 0.2	-33 ± 1.2 (19) P = 0.6
2 control	6.2 ± 0.1 (88)	5.3 ± 0.1 (88)	20.4 ± 0.7 (88)	-54 ± 0.6 (88)	-34 ± 0.6 (88)
lidocaine (1×10^{-5}M)	5.3 ± 0.2 (36) P < 0.001	4.8 ± 0.2 (36) P = 0.02	19.9 ± 1.4 (36) P = 0.7	-53 ± 1.1 (36) P = 0.3	-31 ± 1.3 (36) P = 0.06
lidocaine (2×10^{-5}M)	4.9 ± 0.1 (47) P < 0.001	4.0 ± 0.2 (47) P < 0.001	15.9 ± 1.2 (47) P < 0.001	-55 ± 1.0 (47) P = 0.4	-34 ± 1.3 (47) P = 0.9
lidocaine (4×10^{-5}M)	3.9 ± 0.1 (57) P < 0.001	3.5 ± 0.1 (57) P < 0.001	13.9 ± 0.7 (57) P < 0.001	-52 ± 1.0 (51) P = 0.02	-32 ± 1.0 (51) P = 0.09
5 control	5.1 ± 0.3 (18)	3.7 ± 0.3 (18)	12.8 ± 1.0 (18)	-52 ± 1.5 (18)	-33 ± 0.8 (18)
lidocaine (2×10^{-5}M)	2.9 ± 0.1 (22) P < 0.001	-	-	-52 ± 0.9 (22) P > 0.9	-33 ± 1.1 (22) P > 0.9

TABLE 3

THE EFFECT OF REDUCTION IN EXTERNAL K^+ LEVEL ON THE ACTIONS OF LIDOCAINE ON GUINEA PIG ATRIAL POTENTIALS

Treatment	Spike height mV	Max. diastolic potential mV	Overshoot mV	Max. rate of rise Vs^{-1}	Time to 50% repolarization ms
1. control 2 Hz	90.1 ± 0.9 (60)	70.9 ± 0.7 (57)	19.3 ± 0.5 (57)	151 ± 4.6 (60)	40 ± 0.8 (60)
2. K^+ 2.3 mM	101.8 ± 1.6 (30)	81.3 ± 1.3 (30)	20.5 ± 0.7 (30)	196 ± 6.1 (30)	40 ± 0.6 (30)
1 *versus* 2	P < 0.001	P < 0.001	P = 0.2	P < 0.001	P < 0.9
3. lidocaine (2×10^{-5}M)	87.0 ± 0.9 (61)	69.9 ± 0.7 (60)	17.1 ± 0.7 (60)	117 ± 2.9 (61)	43 ± 1.1 (61)
1 *versus* 3	P = 0.03	P = 0.3	P = 0.01	P < 0.001	P = 0.01
4. lidocaine (2×10^{-5}M) K^+ 2.3 mM	96.3 ± 1.7 (50)	79.8 ± 1.4 (50)	16.5 ± 0.7 (50)	159 ± 4.6 (50)	38 ± 0.5 (50)
3 *versus* 4	P < 0.001	P < 0.001	P = 0.5	P < 0.001	P < 0.001
2 *versus* 4	P = 0.04	P = 0.5	P < 0.001	P < 0.001	P < 0.03

Pooled data from four guinea pigs. Significance of difference of means has been determined by Students "t" test. Comparisons between means are indicated in the "Treatment" column. Stimulus frequency 2 Hz.

TABLE 4

THE EFFECT OF VARIATION IN EXTERNAL K^+ LEVEL ON THE ACTIONS OF LIDOCAINE ON SOME PARAMETERS OF THE ATRIAL POTENTIAL

Treatment	Rate constant, k_1, ms^{-1}	Rate constant, k_2, ms^{-1}	Ionic conductance, g_i mmho cm^{-2}	Excitation potential V* mV	V_{max} mV
1. control	5.7 ± 0.1 (57)	4.9 ± 0.1 (57)	18.6 ± 0.7 (57)	-51 ± 0.7 (55)	-31 ± 0.6 (55)
2. K^+ 2.3 mM	6.3 ± 0.2 (30)	5.2 ± 0.2 (30)	19.6 ± 1.1 (30)	-59 ± 0.8 (30)	-37 ± 0.9 (30)
1 *versus* 2	P = 0.02	P = 0.09	P = 0.4	P < 0.001	P < 0.001
3. lidocaine (2×10^{-5}M)	4.6 ± 0.1 (59)	3.5 ± 0.1 (59)	12.6 ± 0.4 (59)	-52 ± 0.7 (58)	-32 ± 0.7 (58)
1 *versus* 3	P < 0.001	P < 0.001	P < 0.001	P = 0.4	P = 0.2
4. lidocaine (2×10^{-5}M) K^+ 2.3 mM	4.5 ± 0.1 (50)	4.4 ± 0.1 (50)	17.8 ± 0.8 (50)	-57 ± 0.1 (50)	-34 ± 0.8 (50)
3 *versus* 4	P = 0.9	P < 0.001	P < 0.001	P < 0.001	P = 0.06
2 *versus* 4	P < 0.001	P < 0.001	P = 0.2	P = 0.1	P = 0.6

TABLE 5

THE EFFECT OF INCREASE IN EXTERNAL K^+ LEVEL ON THE ACTIONS OF LIDOCAINE ON GUINEA PIG ATRIAL POTENTIALS

Treatment	Spike Height mV	Max. diastolic potential mV	Overshoot mV	Max. rate of rise Vs^{-1}	Time to 50% repolarization ms
1. control 2 Hz	90.7 ± 0.9 (31)	73.1 ± 0.7 (30)	17.7 ± 0.7 (30)	164 ± 5.4 (31)	41 ± 0.9 (31)
2. K^+ 6.9 mM	81.2 ± 1.3 (24)	65.2 ± 1.0 (24)	15.9 ± 1.2 (24)	125 ± 8.0 (24)	40 ± 0.7 (24)
1 *versus* 2	P < 0.001	P < 0.001	P = 0.2	P < 0.001	P = 0.4
3. lidocaine (2×10^{-5}M)	93.1 ± 1.1 (28)	72.7 ± 1.0 (25)	21.0 ± 1.3 (25)	147 ± 6.7 (28)	45 ± 0.6 (28)
1 *versus* 3	P = 0.1	P = 0.6	P = 0.03	P = 0.04	P < 0.001
4. lidocaine (2×10^{-5}M) K^+ 6.9 mM	80.1 ± 0.8 (52)	66.7 ± 0.8 (51)	13.4 ± 0.7 (51)	87 ± 4.0 (52)	44 ± 0.6 (52)
3 *versus* 4	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P = 0.2
2 *versus* 4	P = 0.5	P = 0.3	P = 0.9	P < 0.001	P < 0.001

Procedures as in Table 3. Data from four guinea pigs.

TABLE 6

THE EFFECT OF INCREASE IN EXTERNAL K^+ LEVEL ON THE ACTIONS OF LIDOCAINE ON SOME PARAMETERS OF THE ATRIAL POTENTIAL

Treatment	Rate constant, k_1, ms^{-1}	Rate constant, k_2, ms^{-1}	Ionic conductance, g_i mmho cm^{-2}	Excitation potential V* mV	
1. control	6.2 ± 0.2 (21)	5.2 ± 0.2 (21)	19.7 ± 1.1 (21)	-55 ± 0.6 (21)	-33 ± 0.8 (21)
2. K^+ 6.9 mM	4.3 ± 0.4 (14)	4.5 ± 0.3 (14)	18.6 ± 1.4 (14)	-47 ± 1.3 (14)	-25 ± 1.4 (14)
1 *versus* 2	P < 0.001	P = 0.04	P = 0.5	P < 0.001	P < 0.001
3. lidocaine (2×10^{-5}M)	3.9 ± 0.1 (15)	3.3 ± 0.1 (15)	12.8 ± 0.8 (15)	-57 ± 0.9 (15)	-36 ± 0.9 (15)
1 *versus* 3	P < 0.001	P < 0.001	P < 0.001	P = 0.04	P = 0.1
4. lidocaine (2×10^{-5}M) K^+ 6.9 mM	3.0 ± 0.1 (30)	2.9 ± 0.2 (30)	12.4 ± 1.1 (30)	-50 ± 1.0 (24)	-29 ± 1.2 (24)
3 *versus* 4	P < 0.001	P = 0.1	P = 0.8	P < 0.001	P < 0.001
2 *versus* 4	P < 0.001	P < 0.001	P < 0.001	P = 0.09	P = 0.02

Procedures as in Table 3. Pooled data from three guinea pigs.

TABLE 7

THE EFFECT OF VARIATION IN EXTERNAL K^+ AND Ca^{2+} LEVEL ON THE ACTIONS OF LIDOCAINE

Treatment	Spike height mV	Max. diastolic potential mV	Overshoot mV	Max. rate of rise Vs^{-1}	Time to 50% repolarization ms
1. control 2 Hz	89.3 ± 0.8 (44)	72.9 ± 0.8 (41)	16.7 ± 0.6 (41)	176 ± 5.5 (44)	28 ± 0.6 (44)
2. K^+ 6.9 mM Ca^{2+} 3.6 mM	81.6 ± 2.0 (21)	63.5 ± 1.0 (21)	18.1 ± 1.4 (21)	105 ± 7.1 (21)	25 ± 0.9 (21)
1 *versus* 2	P < 0.001	P < 0.001	P = 0.3	P < 0.001	P = 0.01
3. K^+ 6.9 mM Ca^{2+} 3.8 mM lidocaine (2×10^{-5}M)	76.3 ± 1.3 (38)	59.5 ± 0.9 (38)	17.8 ± 0.7 (38)	86 ± 6.4 (38)	26 ± 0.7 (38)
2 *versus* 3	P = 0.03	P = 0.05	P = 0.1	P = 0.05	P = 0.7

Pooled date from three guinea pigs.

TABLE 8

THE EFFECT OF VARIATION IN EXTERNAL K^+ AND Ca^{2+} LEVEL ON THE ACTIONS OF LIDOCAINE ON SOME PARAMETERS OF THE ACTION POTENTIAL

Treatment	Rate constant, k_1 ms^{-1}	Rate constant, k_2, ms^{-1}	Ionic conductance, g_i mmho cm^{-2}	Excitation potential V* mV	V_{max} mV
1. control 2 Hz	6.1 ± 0.2 (38)	7.0 ± 0.2 (38)	30.9 ± 1.4 (38)	-50 ± 0.8 (36)	-26 ± 0.7 (36)
2. K^+ 6.9 mM Ca^{2+} 3.6 mM	4.4 ± 0.2 (17)	3.7 ± 0.4 (17)	14.6 ± 2.2 (17)	-46 ± 1.3 (17)	-25 ± 1.7 (17)
1 *versus* 2	P < 0.001	P < 0.001	P < 0.001	P = 0.5	P = 0.3
3. K^+ 6.9 mM Ca^{2+} 3.6 mM lidocaine (2×10^{-5}M)	3.2 ± 0.1 (29)	3.3 ± 0.2 (29)	13.7 ± 1.1 (29)	-44 ± 0.7 (29)	-22 ± 1.2 (29)
2 *versus* 3	P < 0.001	P = 0.3	P = 0.6	P = 0.2	P = 0.2

TABLE 9

THE EFFECT OF LIDOCAINE ON RABBIT ATRIOVENTRICULAR POTENTIALS

	Spike height mV	Max. diastolic potential mV	Overshoot mV	Max. rate of rise Vs^{-1}	Time to 50% repolarization ms	Rate min^{-1}
control	53.5 ± 0.9 (104)	49.6 ± 0.9 (99)	3.9 ± 0.8 (99)	8 ± 0.4 (103)	38 ± 0.9 (102)	192 ± 3.5 (26)
lidocaine (2×10^{-5}M)	46.8 ± 1.7 (61) P < 0.001	49.4 ± 1.5 (57) P > 0.9	-3.2 ± 1.3 (57) P < 0.001	6 ± 0.3 (54) P < 0.001	42 ± 1.5 (60) P = 0.02	177 ± 5.9 (14) P = 0.03
control	53.2 ± 1.3 (46)	48.5 ± 1.3 (46)	4.7 ± 1.3 (46)	9 ± 0.4 (46)	37 ± 1.3 (46)	194 ± 5.9 (14)
lidocaine (4×10^{-5}M)	42.9 ± 2.2 (19) P < 0.001	43.6 ± 2.3 (20) P = 0.06	0.3 ± 1.8 (19) P = 0.07	6 ± 0.7 (19) P < 0.001	59 ± 3.3 (19) P < 0.001	179 ± 9.7 (19) P = 0.1

Pooled date from six rabbits.

TABLE 10

THE EFFECT OF LIDOCAINE ON ATRIOVENTRICULAR NODAL POTENTIALS AT A STIMULUS RATE OF 5.5 Hz

Treatment	Spike height mV	Max. diastolic potential mV	Overshoot mV	Max. rate of rise Vs^{-1}	Time to 50% repolarization ms
1. control (spontaneous rate)	59.7 ± 2.2 (30)	53.3 ± 1.6 (29)	7.2 ± 1.3 (29)	12 ± 0.8 (30)	36 ± 1.8 (30)
2. 5.5 Hz	53.5 ± 3.1 (27)	50.3 ± 1.7 (27)	3.2 ± 2.1 (27)	9 ± 0.7 (27)	30 ± 1.4 (25)
1 *versus* 2	P = 0.1	P = 0.2	P = 0.1	P = 0.008	P = 0.02
3. 5.5 Hz lidocaine (2×10^{-5}M)	59.0 ± 2.9 (27)	54.3 ± 2.1 (27)	4.7 ± 1.6 (27)	8 ± 0.9 (27)	33 ± 1.3 (24)
2 *versus* 3	P = 0.2	P = 0.2	P = 0.6	P = 0.6	P = 0.2

Cells driven at 5.5 Hz in the presence of lidocaine showed 2:1 blockade.

TABLE 11

THE EFFECT OF LIDOCAINE ON RABBIT SINOATRIAL NODAL POTENTIALS

Treatment	Spike height mV	Max. diastolic potential mV	Overshoot mV	Max. rate of rise Vs^{-1}	Time to 50% repolarization ms	Rate min^{-1}
control	52.5 ± 0.8 (72)	46.7 ± 0.6 (71)	5.7 ± 0.7 (71)	12 ± 0.6 (72)	58 ± 0.8 (67)	218 ± 4 (18)
lidocaine (2×10^{-5}M)	49.4 ± 1.4 (41) P = 0.04	47.2 ± 1.0 (40) P = 0.6	2.0 ± 0.9 (40) P = 0.004	8 ± 0.6 (41) P = 0.01	55 ± 1.3 (36) P = 0.5	202 ± 3 (11) P = 0.006
control	52.1 ± 1.1 (42)	48.3 ± 0.8 (42)	3.8 ± 0.8 (42)	11 ± 0.5 (42)	58 ± 0.9 (38)	214 ± 5 (12)
lidocaine (4×10^{-5}M)	46.2 ± 1.1 (40) P < 0.001	42.3 ± 0.9 (40) P < 0.001	3.9 ± 0.6 (40) P = 0.9	9 ± 0.7 (40) P = 0.2	58 ± 1.3 (29) P = 0.2	178 ± 1.6 (13) P < 0.001

Pooled data from three rabbits.

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